

**Transplantation of human neural stem cells restores cognition in an immunodeficient rodent model of traumatic brain injury.**

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**Public Summary:**

Traumatic brain injury (TBI) in humans can result in permanent tissue damage and has been linked to cognitive impairment that lasts years beyond the initial insult. Clinically effective treatment strategies have yet to be developed. Transplantation of human neural stem cells (hNSCs) has the potential to restore cognition lost due to injury, however, the vast majority of rodent TBI/hNSC studies to date have evaluated cognition only at early time points, typically <1month post-injury and cell transplantation. Additionally, human cell engraftment and long-term survival in rodent models of TBI has been difficult to achieve due to host immunorejection of the transplanted human cells, which confounds conclusions pertaining to transplant-mediated behavioral improvement. To overcome these shortfalls, we have developed a novel TBI xenotransplantation model that utilizes immunodeficient athymic nude (ATN) rats as the host recipient for the post-TBI transplantation of human embryonic stem cell (hESC) derived NSCs and have evaluated cognition in these animals at long-term (>=2months) time points post-injury. We report that immunodeficient ATN rats demonstrate hippocampal-dependent spatial memory deficits (Novel Place, Morris Water Maze), but not non-spatial (Novel Object) or emotional/anxiety-related (Elevated Plus Maze, Conditioned Taste Aversion) deficits, at 2-3months post-TBI, confirming that ATN rats recapitulate some of the cognitive deficits found in immunosufficient animal strains. Approximately 9-25% of transplanted hNSCs survived for at least 5months post-transplantation and differentiated into mature neurons (NeuN, 18-38%), astrocytes (GFAP, 13-16%), and oligodendrocytes (Olig2, 11-13%). Furthermore, while this model of TBI (cortical impact) targets primarily cortex and the underlying hippocampus and generates a large lesion cavity, hNSC transplantation facilitated cognitive recovery without affecting either lesion volume or total spared cortical or hippocampal tissue volume. Instead, we have found an overall increase in host hippocampal neuron survival in hNSC transplanted animals and demonstrate that a correlation exists between hippocampal neuron survival and cognitive performance. Together, these findings support the use of immunodeficient rodents in models of TBI that involve the transplantation of human cells, and suggest that hNSC transplantation may be a viable, long-term therapy to restore cognition after brain injury.

**Scientific Abstract:**

Traumatic brain injury (TBI) in humans can result in permanent tissue damage and has been linked to cognitive impairment that lasts years beyond the initial insult. Clinically effective treatment strategies have yet to be developed. Transplantation of human neural stem cells (hNSCs) has the potential to restore cognition lost due to injury, however, the vast majority of rodent TBI/hNSC studies to date have evaluated cognition only at early time points, typically <1month post-injury and cell transplantation. Additionally, human cell engraftment and long-term survival in rodent models of TBI has been difficult to achieve due to host immunorejection of the transplanted human cells, which confounds conclusions pertaining to transplant-mediated behavioral improvement. To overcome these shortfalls, we have developed a novel TBI xenotransplantation model that utilizes immunodeficient athymic nude (ATN) rats as the host recipient for the post-TBI transplantation of human embryonic stem cell (hESC) derived NSCs and have evaluated cognition in these animals at long-term (>=2months) time points post-injury. We report that immunodeficient ATN rats demonstrate hippocampal-dependent spatial memory deficits (Novel Place, Morris Water Maze), but not non-spatial (Novel Object) or emotional/anxiety-related (Elevated Plus Maze, Conditioned Taste Aversion) deficits, at 2-3months post-TBI, confirming that ATN rats recapitulate some of the cognitive deficits found in immunosufficient animal strains. Approximately 9-25% of transplanted hNSCs survived for at least 5months post-transplantation and differentiated into mature neurons (NeuN, 18-38%), astrocytes (GFAP, 13-16%), and oligodendrocytes (Olig2, 11-13%). Furthermore, while this model of TBI (cortical impact) targets primarily cortex and the underlying hippocampus and generates a large lesion cavity, hNSC transplantation facilitated cognitive recovery without affecting either lesion volume or total spared cortical or

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